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| EXAMINER | |
|---|---|
| BERTAGNA, ANGELA MARIE | |
| ART UNIT | PAPER NUMBER |
| 1637 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/532,975 | MITANI ET AL. | |
| | Examiner | Art Unit | |
| | Angela Bertagna | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application*

1. Applicant's response filed on November 15, 2007 is acknowledged. Claims 1-21 are currently pending. In the response, Applicant amended claims 1, 7, 9, and 16. Claims 18-21 are withdrawn from consideration as being drawn to a non-elected invention. The following are new grounds of rejection necessitated by Applicant's amendments to the claims. Accordingly, this Office Action is made FINAL.

### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-7 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabbani et al. (EP 0 971 039 A2; cited previously) in view of Notomi et al. (Nucleic Acids Research 2000; 28(12): e63; cited on an IDS).

Regarding claim 1, Rabbani teaches a method for amplifying a nucleic acid comprising:

(a) providing a primer comprising in its 3' end portion a sequence (Ac') that hybridizes to a sequence (A) in the 3'end portion of the target nucleic acid, and a sequence (B') located 5' of (Ac') that hybridizes to the complementary sequence (Bc) of a sequence (B) positioned 5' of sequence (A) in the target nucleic acid (see Example 1 on page 21, where the FC and RC primers of Rabbani are taught; see also Figure 1 for a schematic of the primers binding to a target)

wherein in the absence of an intervening sequence between (Ac') and (B'), (X-Y)/X is between –1.00 and 1.00, where X is the number of bases in sequence (Ac') and Y is the number of bases in the region flanked by sequences (A) and (B) on the target nucleic acid sequence (see Example 1 on page 21, paragraphs 117-118, where the FC and RC primers have an (Ac') region of 29 or 30 nucleotides and the region flanked by sequences A and B is 0 nucleotides, since there is no intervening sequence between them. Therefore, (X-Y)/X = (29-0)/29 = 1)

(b) providing a template nucleic acid (page 21, paragraphs 117 and 120)

(c) annealing the primer to the template and synthesizing a nucleic acid sequence complementary to the target by primer extension (see paragraph 120-121 and also Figure 1, steps 1-2)

(d) hybridizing sequence (B') with sequence (Bc) on the newly synthesized strand, thereby allowing sequence (A) on the target strand to be single-stranded (see Figure 1, step 3)

(e) annealing another primer of step (a) to the single-stranded sequence (A) on the target generated in step (d) and conducting a strand displacement reaction, thereby displacing the complementary nucleic acid synthesized in step (c) (see Figure 1, steps 4-5).

Regarding claim 2, Rabbani teaches that the double-stranded nucleic acid obtained in step (e) is used repeatedly in step (d) (see Figure 1 and paragraph 47).

Regarding claims 3 and 12, Rabbani teaches that the method is conducted isothermally (see paragraphs 46, 51, and 121).

Regarding claims 4 and 13, Rabbani teaches use of the Bst DNA polymerase, which has strand-displacing ability (paragraph 120).

Regarding claims 5 and 14, Rabbani teaches that the method further comprises a step of synthesizing cDNA with a reverse transcriptase from an RNA template (paragraph 111).

Regarding claims 6, 7, 15, and 16, Rabbani teaches conducting the method in the presence of a melting temperature adjusting agent, specifically formamide or DMSO (paragraph 39).

Regarding claim 9, Rabbani teaches a method for amplifying a target nucleic acid in a double-stranded template nucleic acid comprising:

(a) providing a first primer comprising in its 3' end portion a sequence (Ac') that hybridizes to a sequence (A) in the 3'end portion of the target nucleic acid, and a sequence (B') located 5' of (Ac') that hybridizes to the complementary sequence (Bc) of a sequence (B) positioned 5' of sequence (A) in the target nucleic acid (see Example 1 on page 21, where the FC and RC primers of Rabbani are taught; see also Figure 1 for a schematic of the primers binding to a target)

wherein in the absence of an intervening sequence between (Ac') and (B'), (X-Y)/X is between –1.00 and 1.00, where X is the number of bases in sequence (Ac') and Y is the number of bases in the region flanked by sequences (A) and (B) on the target nucleic acid sequence (see Example 1 on page 21, paragraphs 117-118, where the FC and RC primers have an (Ac') region of 29 or 30 nucleotides and the region flanked by sequences A and B is 0 nucleotides, since there is no intervening sequence between them. Therefore, (X-Y)/X = (29-0)/29 = 1)

(b) providing a second primer comprising in its 3' end portion a sequence (Cc') that hybridizes to a sequence (C) in the 3'end portion of the target nucleic acid, and a sequence (D') located 5' of (Cc') that hybridizes to the complementary sequence (Dc) of a sequence (D) positioned 5' of sequence (C) in the target nucleic acid (see Example 1 on page 21, where the FC and RC primers of Rabbani are taught; see also Figure 1 for a schematic of the primers binding to a target)

wherein in the absence of an intervening sequence between (Cc') and (D'), (X-Y)/X is between –1.00 and 1.00, where X is the number of bases in sequence (Cc') and Y is the number of bases in the region flanked by sequences (C) and (D) on the target nucleic acid sequence (see Example 1 on page 21, paragraphs 117-118, where the FC and RC primers have an (Cc') region of 29 or 30 nucleotides and the region flanked by sequences C and D is 0 nucleotides, since there is no intervening sequence between them. Therefore, (X-Y)/X = (29-0)/29 = 1)

(c) providing a double-stranded template nucleic acid consisting of the first and second template strands (paragraphs 77 and 117)

(d) annealing the first and second primers to the first and second template nucleic acids and synthesizing complementary strands via primer extension (paragraphs 117-118; see Figure 1,

steps 1-2 for a schematic of how the primers anneal to the target. Although Figure 1 shows the reactions occurring on only one strand, when both the FC and RC primer are used with a double-stranded template as taught by Rabbani in Example 1, each of the primers inherently undergoes the reactions outlined in Figure 1 on a different strand of the template; see also paragraph 77, where Rabbani expressly teaches conducting the amplification method using two stem-loop primers each of which is complementary to a different strand of a double-stranded DNA template)

(e) hybridizing the sequences (B') and (D') with the newly synthesized sequences (Bc) and (Dc), respectively, thereby making sequences (A) and (C) single stranded (see Figure 1, step 3 and paragraph 118; see also paragraph 77)

(f) annealing primers having the same sequence as the first and second primers of step (a) to sequences (A) and (C) obtained in step (e) above and conducting strand displacement polymerization to displace the complementary strands obtained in step (d) and synthesize new complementary strands (see paragraph 118 and Figure 1, steps 4-5; see also paragraph 77).

Regarding claim 10, Rabbani teaches that the double-stranded nucleic acids obtained in step (f) are repeatedly used in step (e) (see paragraphs 77 & 118; see also Figure 1).

Regarding claim 11, Rabbani teaches that the first and second complementary nucleic acids obtained in step (f) as single-stranded nucleic acids are used repeatedly as template nucleic acids in step (d) (see Figure 2, step 4 and paragraph 77).

In the method of Rabbani, the primers have a value of (X-Y)/X = 1.00, which lies outside the claimed range of -1.00 to 0.50.

Notomi teaches a method for isothermally amplifying DNA using primers that form stem-loop structures after extension (see abstract, pages ii-iv, and Figure 1). Like the primers of Rabbani, the primers of Notomi comprise a region that is complementary to the template and a region that is complementary to a portion of the primer extension product (see pages ii-iv and Figure 1). Regarding claims 1 and 9, Notomi teaches that the size of the loop formed between the primer and the primer extension product is critical to the efficiency of the amplification method, and that a loop of 40 bases or longer gave the best results (page v, column 1). Since the template-complementary region of the primers of Rabbani is 29 or 30 nucleotides (see above), separation of the two regions bound by the two portions of these primers would result in (X-Y)/X = (29-40)/40 = -0.38 or (X-Y)/X = (30-40)/30 = -0.33. These values are within the claimed range of -1.00 to 0.50.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Notomi to the method taught by Rabbani. An ordinary artisan would have been motivated to optimize the length of the loop formed by the primer taught by Rabbani, since Notomi taught that this parameter was critical to achieving optimal amplification efficiency (see page v, column 1). Furthermore, since Notomi taught that a loop of at least 40 nucleotides was optimal to achieving optimal amplification efficiency, application of these teachings to the method of Rabbani would have yielded primers with the claimed properties (see above). Finally, attention is directed to *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) which states, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not inventive, and no evidence has been submitted to

suggest that the selection of the claimed range was other than routine or that the results should be considered unexpected compared to the closest prior art of Rabbani. Thus, the methods of claims 1-7 and 9-16 are *prima facie* obvious over Rabbani in view of Notomi in the absence of secondary considerations.

4. Claims 8 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabbani et al. (EP 0 971 039 A2; cited previously) in view of Notomi et al. (Nucleic Acids Research 2000; 28(12): e63; cited on an IDS) and further in view of Kool, E.T. (Current Opinion in Chemical Biology (2000) 4: 602-608; cited previously).

The combined teachings of Rabbani and Notomi result in the methods of claims 1-7 and 9-16, as discussed above.

Neither Rabbani nor Notomi teaches that target nucleic acid sequence in the template nucleic acid comprises non-natural nucleotides as required by claims 8 and 17.

Kool teaches methods of using modified DNA templates as substrates for DNA polymerases. Kool teaches that DNA polymerases can accept synthetic modifications to the template or newly synthesized strand (page 602, column 2). Kool further teaches that templates containing nucleotides with altered hydrogen-bonding capabilities may be amplified by DNA polymerase (page 604). Kool teaches that the presence of these non-native nucleotides in the template strand directs non-specific incorporation of any of the four natural bases into the newly synthesized strand, which is useful for mutagenesis (page 604).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to conduct the amplification method resulting from the combined teachings of Rabbani

and Notomi using a template containing non-natural nucleotide. An ordinary artisan would have been motivated to do so, because Kool taught that the inclusion of such nucleotides in the template strand was useful for mutagenesis applications (see page 604). Since Kool further taught a number of specific examples of non-native nucleotides that could be recognized and amplified by DNA polymerases (see pages 604-606), an ordinary artisan would have had a reasonable expectation of success in utilizing a template containing non-native nucleotides in the method resulting from the combined teachings of Rabbani and Notomi. Thus, the methods of claims 8 and 17 are *prima facie* obvious over Rabbani in view of Notomi and further in view of Kool.

***Terminal Disclaimer***

5. The terminal disclaimer filed on November 15, 2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent issued from co-pending application 10/583,706 has been reviewed and is accepted. The terminal disclaimer has been recorded.

***Response to Arguments***

6. Applicant's arguments, see page 9, filed on November 15, 2007, with respect to the objections to the specification, have been fully considered and are persuasive. Applicant's amendment overcomes the objections, and therefore, they have been withdrawn.

Applicant's arguments, see page 9, filed on November 15, 2007, with respect to the objection to claim 7, have been fully considered and are persuasive. Applicant's amendment overcomes the objection, and therefore, it has been withdrawn.

Applicant's arguments, see pages 9-10, filed on November 15, 2007, with respect to the rejection of claims 1-7 and 9-16 under 35 U.S.C. 102(b) as being anticipated by Rabbani, have been fully considered and are persuasive. Rabbani does not teach all of the elements of the amended claims, and therefore, the rejection been withdrawn.

Applicant's arguments, see page 11, filed on November 15, 2007, with respect to the rejection of claims 8 and 17 under 35 U.S.C. 103(a) as being unpatentable over Rabbani in view of Kool, have been fully considered and are persuasive. This rejection has been withdrawn.

## *Conclusion*

7. No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

1/29/08